The Dutch guidelines for Marfan syndrome: ‘between evidence and common sense’

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Outline

1. Introduction on Marfan clinics in the Netherlands

2. Quiz to test your knowledge about Marfan syndrome

3. Some Marfan facts and figures

4. Development of the Dutch Marfan guidelines

5. Marfan guidelines: evidence, expert opinion or common sense ...

6. Conclusions and questions
The Marfan Quiz
Marfan clinics and DNA-diagnostics in the Netherlands

- Groningen
- Nijmegen
- Maastricht
- Amsterdam (AMC)
- Amsterdam (VUMC)
- Leiden
- Rotterdam
Marfan facts - Skeletal features

Pectus deformities

Arachnodactyly (spider fingers)

Flat feet with hindfoot deformity

Pictures from National Marfan Foundation
Tall stature with long limbs
Marfan facts - Facial characteristics

- downslant of palpebral fissures
- long face

Vincent Schiavelli in “One flew over the cuckoo’s nest”

high palate and crowding of teeth
Marfan facts - Cardiovascular features

- 83% aortic root dilatation and 88% MVP before age 25
- 20% cardiac surgery for aortic regurgitation or severe aortic root dilatation before age 25

Survival from 40 to approximately 70 years
Marfan facts - Ophthalmologic features

Ectopia lentis: 40-87%

Myopia > 3D bij 50%
Marfan facts - Molecular aspects and pathogenesis

The gene: \( FBN1 \)

- > 95% of Marfan
- Autosomal dominant
- 25% de novo

Release of proteases: MMP2 and MMP9

Matrix proteolysis

Aortic smooth muscle cell

Altered TGFβ responsive gene expression?

Increased Smad nuclear localization

Increased Smad2/3 phosphorylation

Active TGFβ

Fibrillin-1

Proline-rich region (fibrillin-1)

Elastin

Microfibril sheath

Matrix fibers

Elastic fiber
Development of the Dutch guidelines

Start in June 2010

Finish in December 2012
Why guidelines?

To create a tool for the provision of uniform care in Marfan syndrome

- Referral
- Diagnosis
- Family studies
- Surveillance
- Organization Marfan clinic
- Treatment
- Prenatal diagnosis
- Pregnancy and delivery
Working group

1. Cardiothoracic surgeon
2. Clinical geneticist
3. Gynaecologist
4. Cardiologist
5. Molecular geneticist
6. Pediatric cardiologist
7. Ophthalmologist
8. Orthopedic surgeon
9. Dutch patients association for Marfan syndrome

Methodologic support of a senior advisor of Dept of Professional Quality Support of the Dutch Federation of Medical Specialists (FMS)
Development of the guidelines

Appraisal of Guidelines for Research & Evaluation II" (AGREE II) instrument (www.agreecollaboration.org)

- Clinical question
- Literature search (EBRO-methodology)
- Summary of literature
- Conclusions
- Considerations
- Recommendations

- Expertise
- Patient preferences
- Costs
- Availability of facilities
- Organizational aspects
Evidence, expert opinion or common sense

Evidence according to the EBRO classification

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Diagnostic accuracy of research</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Meta-analysis of two A2 studies</td>
</tr>
<tr>
<td>A2</td>
<td>Gold standard research: prospective, sufficient size, control group</td>
</tr>
<tr>
<td>B</td>
<td>Prospective but not with all features of A2, retrospective study or case-control study</td>
</tr>
<tr>
<td>C</td>
<td>Non comparative study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conclusion based on</th>
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<tbody>
<tr>
<td>1</td>
<td>One study A1 or two A2</td>
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<tr>
<td>2</td>
<td>One study A2 or two B</td>
</tr>
<tr>
<td>3</td>
<td>One study B or C</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
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Clinical question
What’s the effect of certain drugs on aortic growth?

Literature search and summary of literature
✓ β-blokkers: positive effect but not conclusively proven
✓ Losartan: showed an positive effect in severe pediatric marfan patients

Conclusions
✓ β-blokkers: there are indications for an inhib. effect on the growth of the aorta
✓ Losartan: research just started, indication that it might work

Considerations
✓ Adverse effects
✓ No undisputable proof

Recommendations
✓ β-blockers: prescribe till more evidence
✓ Losartan: not proven yet, be conservative in prescribing
The Dutch guidelines

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Who should be referred?
The basketball team

One of the mates of this basketball team died suddenly of an acute aortic dissection. The coach is worried, he heard this boy might have been affected with Marfan. He wants all players to be screened at a marfan clinic.

Question:
What is your advice?
A. You advice to screen all men just to be sure
B. You tell the coach not to worry. Marfan is a rare disorder, the chance that one of the team mates is affected is low
One of the men is still worried. Hij is tall and skinny but has no other marfanoid features. His family history is negative for aortic disease. He visits his GP.

**Question:**
What would be wise for the GP to advice?
A. Reassure
B. Only refer to a marfan clinic if there are more features
C. Always refer to a marfan clinic or expert
What’s in the Dutch guidelines?

**Recommendations (Ch 3 Diagnostics)**

I. Refer all patients with the following features for assessment by a specialist in Marfan syndrome, preferably in association with a Marfan clinic:
- Aortic root dilatation or dissection of the thoracic aorta without obvious cause, or
- (Sub)luxation of the lens, or
- First-degree relative with Marfan syndrome.

II. Refer patients with **less specific features** of Marfan syndrome to an experienced specialist in Marfan syndrome, assessing the appropriate diagnostic route based on the features.
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Criteria for diagnosis and Z-scores
The revised Ghent nosology for the Marfan syndrome

Bart L Loeys,1 Harry C Dietz,2 Alan C Braverman,3 Bert L Callewaert,1
Julie De Backer,1 Richard B Devereux,4 Yvonne Hilhorst-Hofstee,5
Guillaume Jondeau,6 Laurence Faivre,7 Dianna M Milewicz,8 Reed E Pyeritz,9
Paul D Sponseller,10 Paul Wordsworth,11 Anne M De Paepe1

J Med Genet juni 2010
Diagnosis of Marfan syndrome

Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

In the absence of family history:

1. Ao (Z ≥ 2) AND EL = MFS*
2. Ao (Z ≥ 2) AND FBN1 = MFS
3. Ao (Z ≥ 2) AND Syst (≥ 7pts) = MFS*
4. EL AND FBN1 with known Ao = MFS
Sarah 40 yr was admitted to a marfanclinic because she is very tall, she has long fingers and a scoliosis. She has a disporportionate body habitus with long arms and legs.

Height 192 cm and weight **100 kg**

BSA: 2.3

Aortic root 43 mm

Systemic score 7

Eye examination normal
Your opinion

If you were the coördinating doctor of the marfanclinic, would you tell her:

A. Not to worry, she does not fullfill the criteria for Marfan
B. She might have Marfan syndrome and you want to do further examinations

Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

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4. EL AND FBN1 with known Ao=MFS
Z-score or absolute diameter?

Assumption of a linear relationship BSA – aortic root.

adult > 40 years old

Roman et al 1989
Sara lost a lot of weight, now she is 192 cm tall and 75 kg
BSA: 2.0
Aortic root 43 mm dilated
Z-score or absolute diameter?

Non-linear relation between aortic root and BSA in 1922 athletes.
(Kinoshita et al. Am Heart J 2000)
New Z-scores

- Height seems to correlate more with aortic root diameter than weight
- In new Z-score calculators the Z-score is less influenced by body weight or BMI

Devereux, 2012; Van Kimmenade 2013

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**Big Sarah**

**Z-SCORE CALCULATION**

Different methods are used for aortic root dilation in different publications (e.g., end-diastolic versus ejection measurement, inner to inner vs. leading edge to leading edge diameter). One should take into account these differences when choosing a formula to calculate Z-scores. Aortic root refers to the measurement at the annulus of valve.

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<tr>
<td>Height (cm): 150</td>
<td>Height (cm): 190</td>
</tr>
<tr>
<td>Weight (kg): 70</td>
<td>Weight (kg): 75</td>
</tr>
<tr>
<td>Age (years): 10</td>
<td>Age (years): 15</td>
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<tr>
<td>TWA: 2.3</td>
<td>TWA: 2.5</td>
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<tr>
<td>Ao Root at sinuses of valve (cm): 4.3</td>
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**Thin Sarah**

**Z-SCORE CALCULATION**

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**Devereux, 2012, calculator on www.marfan.org**
What’s in the Dutch guidelines?

**Recommendations** (Ch 4 Diagnostic imaging aorta)

In an adult, an aortic root >40 mm should generally be regarded as dilated

- Smaller diameters may be considered abnormal depending on age, BSA and sex:
  - Shape of aortic root: pear
  - Ratio aortic root/ascending aorta
  - Z-scores may be helpful

- In children: use Z-scores
The Dutch guidelines

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Treatment of skeletal abnormalities

Should we treat musculoskeletal problems in Marfan patients different from non-Marfan patients?
Scoliosis

Boy 13 years old
Marfan syndrome
Spinal curve 30 degrees

Girl 13 years old
No Marfan syndrome
Spinal curve 30 degrees
Would you think that the scoliosis treatment for patient A with Marfan syndrome is different from patient B without Marfan syndrome?

A. YES
B. NO
Conclusions

<table>
<thead>
<tr>
<th>Level</th>
<th>Statement</th>
<th>Evidence</th>
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<tr>
<td>Level 3</td>
<td>There are indications that, in Marfan patients with a still immature skeleton (Risser 2 or less) and scoliosis curves of between 20 and 45 degrees, wearing a brace can avoid the need for surgery in a small proportion of patients.</td>
<td>C Sponseller et al., 2000; Birch &amp; Herring, 1987</td>
</tr>
<tr>
<td>Level 3</td>
<td>There are indications that the percentage of patients in whom a brace can prevent surgery is lower in Marfan than in non-Marfan patients.</td>
<td>C Sponseller et al. 2000; Birch &amp; Herring, 1987</td>
</tr>
<tr>
<td>Level 4</td>
<td>There is insufficient available literature to justify treating other skeletal abnormalities in Marfan syndrome differently to those in patients without Marfan syndrome.</td>
<td>D Opinion of the working group</td>
</tr>
</tbody>
</table>
What’s in the Dutch guidelines?

Recommendations

In general, treat abnormalities of the musculoskeletal system in patients with Marfan syndrome in the same manner as for patients without Marfan syndrome.

In Marfan patients with scoliosis of between 20 and 45 degrees and a still immature skeleton, the (low) expected success rate of a brace should be weighed against the discomfort and the advantages and disadvantages of an operation.

Ch 6 Treatment skeletal abnormalities
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What are the restrictions?
Emma 13 years old was diagnosed with Marfan syndrome after her father suffered from an acute aortic dissection at age 40 years. She is a quite fanatic competition swimmer.
Your opinion

Emma was bullied at the elementary school because of her glasses and her body habitus. She was very tall and skinny. After she started swimming she got stronger and more confident.

Do you advice Emma to quit her sport?

A. Yes
B. No
What’s in the Dutch guidelines?

**Recommendations** Ch 14 Life style recommendations:
Caution should be exercised with regard to **competitive sports, major peaks of exertion** and intensive static exertion.
Participation in recreational low-to-moderate intensity exercise can usually be allowed.

advice against competitive swimming!
Did the doctor allow Emma to do competitive swimming?

International guidelines based on:
- Expert opinion
- Theoretical considerations
- Retrospective observations

Emma and her parents were informed about the guidelines and together they decided that she was allowed to keep on swimming with stringent follow up at the child cardiologist.

**Inform patient and individualize advice**
Conclusions

- The Dutch guidelines provide a tool to provide uniform care for Marfan patients
- The care for Marfan patients is largely based on expert opinion and common sense
- Guidelines are a guide, the care should be tailored for every patient
- Future research will hopefully provide evidence for several aspects in diagnosis, therapy and surveillance
Acknowledgements

Working group
J.M. Cobben, clinical geneticist
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B.J. Mulder, cardiologist
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B.J. van Royen, orthopedic surgeon
J. Timmermans, cardiologist
J.P. van Tintelen, clinical geneticist

Patient support group
F.M.L.J. Oorthuys, former chair patient support group
QUESTIONS??????

ASK THEM NOW